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demonstrate the similarity between M.V.I.®-12 and Cernevit™ -12 IV Multivitamins.

One noteworthy aspect of the Joyeux study was that patients were excluded from the study if they had received oral or parenteral vitamin supplements one month prior to the study. Shils et.al.[3] required no oral vitamin intake (except vitamin E) for 1 month prior to the study but supplemented patients during that interval with a combination of parenteral vitamin formulations. The multivitamin supplementation by Shils et. al.[3] likely avoided the lower than normal baseline of 1,25 (OH) vitamin D and vitamin E seen by Joyeux, thereby making it easier to achieve levels in the therapeutic range.

2. **Determine the in vivo safety of administration of Cernevit™-12 in patients concomitantly receiving drugs which bind to alpha 1-acid glycoprotein (e.g., propranolol, quinidine, prazosin and disopyramide). An in vitro study by Guentert et. Al. (Br. J. Clin. Pharm. 23: 569-577, 1987), reported a 50-80% increase in the free fraction of drugs known to bind to alpha-1-glycoprotein at therapeutic concentrations of mixed micelles.**

The displacement of drugs bound to AGP by mixed micelles, as demonstrated by Guentert, could theoretically result in an increase in the unbound fraction of that drug *in-vivo*. If this displacement occurred *in-vivo*, a change in the drug kinetics would be expected. Wood et.al.[4] described the effect of drug binding on the volume of distribution, half-life and clearance of the drug. Displacement interactions may increase drug effect, but alterations in drug kinetics would occur in parallel, which may make the situation considerably more complex. Although an initial increase in free fraction and possible pharmacologic effect may be seen, a new steady state between bound and unbound fraction is reached, as long as concomitant therapy continues. The practical importance of displacement interactions depends on factors such as the extent of protein binding and therapeutic index of the bound drug.

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[4] Wood M. Plasma drug binding: implications for anesthesiologists. Anesth. Analg. 1986 (Jul); 65(7): 786-80. A copy of this publication is provided in **Attachment 4** of this communication.

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Kremer et. al.[5] conducted a comprehensive review of drug binding to α_1-acid glycoprotein (AGP). More than 12 different drugs, including disopyramide, propranolol, quinidine, and prazosin have been identified as binding primarily to AGP. Additionally, plasma concentrations of AGP have been reported to vary in over 40 different clinical conditions. For example, Crohn's disease, inflammatory arthritis, and chronic renal failure have been reported to increase plasma drug binding associated with increased AGP levels. Increases in AGP levels have also been associated with smoking, alcohol intake, and obesity. The studies reviewed by Kremer et. al.[5] indicate the large variation in plasma AGP levels observed in response to various physiological, pathological, and environmental conditions can have a profound effect on drug concentrations in the blood. For example, in Table 8 (page 20) of the Kremer publication, a large variation in the free fraction of propranolol was observed in patients studied. This variation is likely attributed to the variation in AGP levels across the different disease states evaluated.

An *in vivo* study to determine the safety of Cernevit™-12 IV Multivitamins in patients concomitantly receiving drugs which bind to α_1-acid glycoprotein would not provide conclusive results because of the number of physiologic, pathologic, and environmental factors which result in fluctuations in AGP plasma concentrations. Furthermore, compounding this variation with the large number of drugs known to bind to AGP would make the study prohibitive. That is, each drug known to bind to AGP would have to be studied in separate trials.

Baxter believes the risk of adverse effects resulting from the concomitant administration of Cernevit™ with AGP binding drugs is minimal. This is based on European and U.S. clinical experience with Cernevit™ since 1988 and knowledge that physicians commonly manage therapy based on patient response. Alternatively, to address the Agency's concerns, Baxter proposes to add an additional statement to the first paragraph of the Drug Interactions subsection of the direction insert for Cernevit™ to highlight the need to monitor patients concomitantly receiving Cernevit™ and AGP binding drugs. The proposed statement follows on the next page and has been underscored for ease of review.

[5] Kremer JM, Wilting J, Janssen LH. Drug binding to human alpha-1-acid glycoprotein in health and disease. Pharmacol Rev. 1988 (Mar);40 (1):1-47. A copy of this publication is provided in **Attachment 5** of this communication.

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Drug Interactions: The dosage of drugs know to be influenced by folic acid and pyridoxine, for example phenytoin and phenobarbital, must be carefully monitored. Pyridoxine can reduce the effect of levodopa. Several drugs are known to influence the serum concentration of vitamins. Consult appropriate references for listings of specific drug vitamin interactions. An *in vitro* study using therapeutic concentrations of glycocholic acid (0.177 mg glycocholate/mL human serum) demonstrated a 50-80% increase in the unbound (free) fraction of drugs known to bind α_1-acid glycoprotein (e.g. disopyramide, propranolol, quinidine, and prazosin). Although the *in vivo* response has not been determined, physicians should closely monitor patients for the possibility of an increase in the therapeutic response to these drugs.

Thank you for incorporating this information into the file. If you have questions or comments, please contact Ms. Linda Coleman or Tamima Itani, Ph.D. at (847) 270-2577.

Sincerely,

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